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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/852,209	05/10/2001	Ulf Eriksson	1064/44740CP	3846

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EXAMINER	
SPECTOR, LORRAINE	

ART UNIT	PAPER NUMBER
1647	

DATE MAILED: 01/16/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/852,209	ERIKSSON ET AL.	
	Examiner	Art Unit	
	Lorraine Spector, Ph.D.	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *14 October 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *36,46-49,59 and 60* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *36,46-49,59 and 60* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ The translation of the foreign language provisional application has been received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *6/4 &6/20/*.
4) ☐ Interview Summary (PTO-413) Paper No(s). _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

Part III: Detailed Office Action

Restriction Requirement:

Applicant's election with traverse of Group IV in Paper filed 10/14/03 is acknowledged. The traversal is on the ground(s) that examination of Group VI would not be a burden. This is found persuasive. Claims 36, 46-49, 59 and 60 will be examined.

Formal Matters:

The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed.

The disclosure is objected to because of the following informalities. Appropriate correction is required for each item listed:

Figure 19 is objected to because two lines are shown, and there is no explanation in the figure nor the brief description of the drawings as to what the lines indicate, respectively. Applicants are reminded to avoid the introduction of new matter.

Figures 13, 14, 20, 26A-26V, 27A-F, 28A-F, 30A-D, 31A-D, 32A-D and 33A-D are objected to because the photocopies submitted are of insufficient quality. No details can be discerned, for example there are numerous blots with no bands visible. It does not appear that legible copies were submitted with the specification as originally filed. If applicants wish to correct the figures, they must point out where basis is found in the specification as originally filed for the information newly conveyed, or in which application that may have been incorporated by reference such basis may be found.

Objections and Rejections under 35 U.S.C. §112:

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 36, 46-49, 59 and 60 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 36, 47 and 49 are indefinite because: (a) the metes and bounds of "analog thereof" cannot be determined, and the specification fails to breath life and meaning into the term, (b) the term "stringent conditions" is not defined in the specification or claims; the metes and bounds of that which will hybridize to a given sequence is dependent upon the precise conditions used. Without specification of such, the metes and bounds of the claims cannot be determined. (c) The claims recite that the fragment or analog has "the biological activity of PDGF-C"; it is not clear to which biological activity the claims refer, as the specification defines numerous biological activities (which definition is itself not limiting of the claims), and also defines biological activity as including inhibitors of PDGF-C itself, which would not be functional in the claimed methods.

Claim 47 is further indefinite because the word "fibroblast" is misspelled in the second line of the claim.

Claims 46 and 48 are indefinite because it cannot be determined whether applicants intend 85% identity to residues 230-345 of SEQ ID NO: 7, or to the entirety of SEQ ID NO: 7.

Claim 48 is further indefinite because the word "alpha" is misspelled in the first line of the claim.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 36, 47, and 49 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The specification discloses the sequences of human and murine PDGF-C and nucleic acids that encode such. However, the rejected claims encompass methods of using an "analog" "having the biological activity of PDGF-C", a protein for which the specification does not provide adequate written description. There is no definition of "analogs", which, in the broadest reasonable interpretation of the term, must be taken to indicate 'functionally equivalent' proteins, nor is there description of species commensurate in scope with the claim to proteins produced by expression of "a polynucleotide comprising a polynucleotide sequence having at least 85% identity" to a specified sequence, or which hybridizes under stringent conditions to a specified sequence. It is noted that a nucleic acid only 85% identical to a recited sequence can encode a protein having as little as 55% identity to the protein encoded by the reference sequence.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See *Vas-Cath* at page 1116).

With the exception of the human and murine sequences referred to above the skilled artisan cannot envision the detailed chemical structure of the encompassed proteins to be used in the claimed methods, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. See *Fiers v. Revel*, 25 USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016.

One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481 at 1483. In *Fiddes*, claims directed to mammalian FGF's were found to be unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence. In this case, the specification provides the murine and human sequences, and seeks coverage for methods of using any protein that is functionally equivalent to such and would be encoded by a polynucleotide that would hybridize under unspecified conditions to a reference molecule.

Therefore, only human and murine PDGF-C, and functional fragments thereof, but not the full breadth of the claims meet the written description provision of 35 U.S.C. §112, first paragraph. Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

Claims 36, 46-49, 59 and 60 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for methods of using human or murine PDGF-C or functional fragments thereof to treat a murine or human species, does not reasonably provide enablement for (a) methods of using proteins that are functional equivalents of such, including "analogs" or proteins 85% identical to the disclosed proteins or proteins encoded by nucleic acids 85% identical to the disclosed nucleic acids, or (b) treatment of any and all mammals or birds. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to the invention commensurate in scope with these claims.

The factors considered when determining if the disclosure satisfies the enablement requirement and whether any necessary experimentation is "undue" include, but are not limited to: 1) nature of the invention, 2) state of the prior art, 3) relative skill of those in the art, 4) level of predictability in the art, 5) existence of working examples, 6) breadth of claims, 7) amount of direction or guidance by the inventor, and 8) quantity of experimentation needed to make or use the invention. *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

The specification does not teach how to make "analogs" of the disclosed PDGF-C receptor, nor functional proteins that are 85% identical to PDGF-C, nor proteins that are as little as 55% identical to such, which would be encoded by nucleic acids 85% identical to those disclosed. There is no definition of "analogs" in the specification as originally filed. The broadest reasonable interpretation of such is that the claims read on all functionally equivalent proteins. The specification discloses human and murine PDGF-C. There is no guidance as to any functional equivalents, nor derivatives, nor are there any working examples of altered sequences that retain PDGF-C function. Accordingly, enablement is not commensurate in scope with claims that encompass 'analogs' of PDGF-C. The Examiner's position is supported by the case law. It was found in *Ex parte Maizel* (27 USPQ2d 1662 at 1665) that:

> Appellants have not chosen to claim the DNA by what it is but, rather, by what it does, i.e., encoding either a protein exhibiting certain characteristics, *or* a biologically functional equivalent thereof. Appellants' claims might be analogized to a single means claim of the type disparaged by the Court of Customs and Patent Appeals in *In re Hyatt,* 708F.2d 712, 218 USPQ 195 (Fed. Cir. 1983). The problem with the phrase "biologically functional equivalent thereof" is that it covers any conceivable means, i.e., cell or DNA, which achieves the stated biological result while the specification discloses, at most, only a specific DNA segment known to the inventor. Clearly the disclosure is not commensurate in scope with the claims."

This case is similar to that in *Ex parte Maizel*, in that applicants have disclosed human and murine PDGF-C, and are claiming methods of using all possible functional equivalents of such. Given the lack of guidance as to functional variants, the lack of direction or working examples, the breadth of the claims, which encompass innumerable possible proteins, and the amount of experimentation required to determine each possible species individually, it would require undue experimentation to use the invention in a manner commensurate in scope with the claims.

With regard to the scope of treating mammals or birds, the specification has only described PDGF-C from "murine" and human species. It is noted that "murine" in this case is mouse; the term "murine", as used in the art, is generic to rats and mice. While it is predictable that other mammals will have PDGF-C homologs, it is not predictable that the disclosed human and mouse homologs would be active in other mammalian species, and there is no guidance, direction or working example as to how to make species that would work in other mammals or birds. The art recognizes that while animals often have homologous genes (i.e. evolutionarily related genes that encode proteins with similar function), the nature of changes in a single protein between species is in any way predictable, nor is it predictable that a homologous protein will have equivalent function in another species. For example, the art appreciates that birds often have proteins homologous to those found in other species, such as human, but which serve distinctly different functions in the avian species. For example, it is known in the art that exogenous growth hormone exerts a lipolytic effect in mammals, but a lipogenic effect in chickens (see L.A. Cogburn et al., Journal of Nutrition 119:1213 for example). Even within a species, closely related proteins can have divergent function the relevant literature reports examples of polypeptide families wherein individual members have distinct, and sometimes even

opposite, biological activities. For example, Tischer et al. (U.S. Patent 5,194,596) establishes that VEGF (a member of the PDGF, or platelet-derived growth factor, family) is mitogenic for vascular endothelial cells but not for vascular smooth muscle cells, which is opposite to the mitogenic activity of naturally occurring PDGF which is mitogenic for vascular smooth muscle cells but not for vascular endothelial cells (column 2, line 46 to column 3, line 2). The differences between PDGF and VEGF are also seen *in vivo*, wherein endothelial-pericyte associations in the eye are disrupted by intraocular administration of PDGF but accelerated by intraocular administration of VEGF (Benjamin et al., 1998, Development 125:1591-1598; see Abstract and pp. 1594-1596). Given the lack of description of PDGF-C from species other than mouse or human, the lack of guidance, direction or working examples, and the state of the art being that it is unpredictable what the equivalent protein, if any, from other species would be or what function it would have, it would require undue experimentation to make PDGF-C within the metes and bounds of the claims that would be reasonably expected to have the desired effect in mammals other than humans or mice, or in birds.

Rejections Over Prior Art:

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

Claims 36, 46-49, 59 and 60 are rejected under 35 U.S.C. 102(a) as being anticipated by Ferrara et al., U.S. Patent Number 6,391,311, cited by applicants.

Ferrara et al. teach human PDGF-C, which they call VEGF-E. The nucleic acid of SEQ ID NO: 6 of the instant application is 83.5% identical to SEQ ID NO: 1 of Ferrara et al. (which would meet the hybridization limitations of claim 31) , and the protein of SEQ ID NO: 7 is 87% identical to SEQ ID NO: 2 of Ferrara et al. The protein of Ferrara's SEQ ID NO: 2 differs from

SEQ ID NO: 3 of the instant application only at two amino acids. Ferrara et al. disclose that VEGF-E is useful for wound repair (abstract) as well as vascular injuries, and induces both vasculogenesis and angiogenesis (column 1, lines 57-65), and demonstrated activity in causing myocyte hypertrophy, fibroblast proliferation, and survival of HUVEC, see columns 28-29. Homo- and heterodimers are disclosed at column 16. With respect to the limitation of claims 48-49 that the method is to "induce PDGF alpha receptor activation", the effect is inherent to the methods disclosed by Ferrara et al., especially as the instant specification does not teach any reason for doing so that is not concordant with Ferrara et al's teachings. Accordingly, the claims are anticipated by Ferrara et al.

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure.

Gao et al., U.S. Patent Number 6,432,673 discloses and claims truncated ZVEGF3. Methods of using the protein consistent with those claimed herein are disclosed. Gao et al. disclosed the full-length and truncated forms of human PDGF-C, which they named ZVEGF3, in their earliest priority application, having filing date 12/7/1998.

The truncated form of PDGF-C disclosed as being active in the instant specification consists of residues 230-345. The instant claims merit priority to at least provisional application 60/110749, filed 12/3/98. which discloses at least a partial human clone, encoding a protein having residues 29-345. Application serial number 60/113,002, filed 12/18/1998, contains the earliest disclosure of full-length human PDGF-C. Neither application discloses the truncated form of PDGF-C having residues 230-345.

Advisory Information:

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Lorraine M. Spector, whose telephone number is (703) 308-

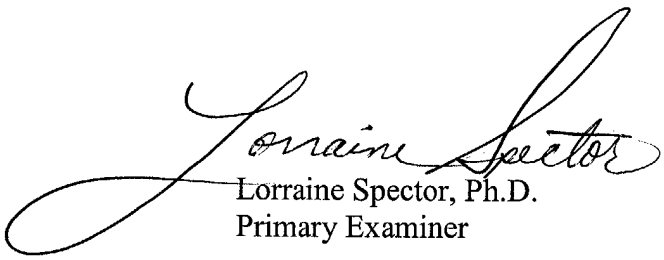
1793. Dr. Spector can normally be reached Monday through Friday, 9:00 A.M. to 5:30 P.M. ***Effective 1/21/2004, Dr. Spector's telephone number will be 571-272-0893.***

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Dr. Gary L. Kunz, at (703)308-4623. ***Effective 1/21/2004, Dr. Kunz' telephone number will be 571-272-0887.***

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist at telephone number (703) 308-0196.

Certain papers related to this application may be submitted to Group 1800 by facsimile transmission The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 C.F.R. § 1.6(d)). NOTE: If Applicant does submit a paper by fax, the original signed copy should be retained by applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED so as to avoid the processing of duplicate papers in the Office.

Official papers filed by fax should be directed to (703) 872-9306 (before final rejection) or (703)872-9307 (after final). Faxed draft or informal communications with the examiner should be directed to (703) 746-5228. ***Effective 1/21/2004, Dr. Spector's fax number will be 571-273-0893.***



Lorraine Spector, Ph.D.
Primary Examiner

12/30/2003